The Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) Trial: Rationale for Its Methodology and a Review of the Effectiveness of Switching Antipsychotics

Stefan Leucht*1, Inge Winter-van Rossum2, Stephan Heres1, Celso Arango1, W. Wolfgang Fleischhacker4, Birte Glenthøj5, Marion Leboyer6, F. Markus Leweke7, Shôn Lewis8, Phillip McGuire9, Andreas Meyer-Lindenberg7, Dan Rujescu10, Shitij Kapur9, René S. Kahn2, and Iris E. Sommer2

1Department of Psychiatry, Psychotherapy and Psychosomatics Martin-Luther-University Halle-Wittenberg, Halle, Germany; 2Department of Psychiatry, Brain Center Rudolf Magnus, Utrecht, The Netherlands; 3Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón, IISGM, School of Medicine, Universidad Complutense, CIBERSAM, Madrid, Spain; 4Biological Psychiatry Division, Department of Psychiatry and Psychotherapy, Medical University Innsbruck, Innsbruck, Austria; 5Center for Neuropsychiatric Research & Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Copenhagen University Hospital, Psychiatric Hospital Center Glostrup, Glostrup, Denmark; 6INSERM U955, Translational Psychiatry Team, Créteil, France, Paris Est University, DHU Pe-PSY, Pôle de Psychiatrie des Hôpitaux Universitaires H Mondor, Créteil, France, Fondation FondaMental; 7Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; 8University of Manchester, Manchester, UK; 9Department of Psychological Medicine, King’s College London, Institute of Psychiatry, London, UK; 10Department of Psychiatry, Psychotherapy and Psychosomatics Martin-Luther-University Halle-Wittenberg, Halle, Germany

*To whom correspondence should be addressed; Department of Psychiatry and Psychotherapy, Technische Universität München, Klinikum rechts der Isar, München, Germany, e-mail: Stefan.Leucht@lrz.tum.de

Background: Most of the 13 542 trials contained in the Cochrane Schizophrenia Group’s register just tested the general efficacy of pharmacological or psychosocial interventions. Studies on the subsequent treatment steps, which are essential to guide clinicians, are largely missing. This knowledge gap leaves important questions unanswered. For example, when a first antipsychotic failed, is switching to another drug effective? And when should we use clozapine? The aim of this article is to review the efficacy of switching antipsychotics in case of nonresponse. We also present the European Commission sponsored “Optimization of Treatment and Management of Schizophrenia in Europe” (OPTiMiSE) trial which aims to provide a treatment algorithm for patients with a first episode of schizophrenia.

Methods: We searched Pubmed (October 29, 2014) for randomized controlled trials (RCTs) that examined switching the drug in nonresponders to another antipsychotic. We described important methodological choices of the OPTiMiSE trial. Results: We found 10 RCTs on switching antipsychotic drugs. No trial was conclusive and none was concerned with first-episode schizophrenia. In OPTiMiSE, 500 first episode patients are treated with amisulpride for 4 weeks, followed by a 6-week double-blind RCT comparing continuation of amisulpride with switching to olanzapine and ultimately a 12-week clozapine treatment in non-remitters. A subsequent 1-year RCT validates psychosocial interventions to enhance adherence. Discussion: Current literature fails to provide basic guidance for the pharmacological treatment of schizophrenia. The OPTiMiSE trial is expected to provide a basis for clinical guidelines to treat patients with a first episode of schizophrenia.

Key words: first episode/schizophrenia/amisulpride/olanzapine/algorithm/nonresponse

Introduction

Schizophrenia is a complex disorder frequently leading to early disability and extensive costs for national health systems. Major efforts are being undertaken to understand its pathophysiology and to improve outcome. To illustrate this effort, the specialized register of the Cochrane Schizophrenia Group contains 13 542 controlled studies (February 2012, https://szg.cochrane.org/cszg-specialised-register). However, the vast majority of these trials have investigated the general efficacy of pharmacological or psychosocial interventions. Very few prospective, sequential studies are available that could guide decisions which have to be made in every day clinical routine. Some of the simplest questions of clinicians remain unanswered. For example: If the first antipsychotic used has not worked, is switching to another drug effective? Or
should we perhaps increase the dose? And when should we start clozapine, the most efficacious drug?

These questions are most urgent for patients with a first episode of schizophrenia, as the duration of untreated psychosis is an important predictor of outcome. First-episode patients on average respond better and faster to antipsychotic drugs. Needs lower doses and have a better prognosis than chronic patients. The first episode is therefore a critical junction in the lives of people with schizophrenia where optimal treatment could positively influence the long-term course.

The European Commission has funded the multinational, multicenter, 3-phase, randomized, double-blind “Optimization of First Episode” (OPTiMiSE, http://www.optimisetrial.eu/) study which is one of the rare studies to test treatment algorithms. Five hundred participants with a first episode of schizophrenia will be treated for a maximum of 22 weeks according to a pharmacological algorithm including a double-blind phase on switching to a second antipsychotic vs continuation of the first, as well as an early use of clozapine in nonremitters. These interventions will be coupled with several other work packages to provide an extensive examination of potential biological predictors of response and a subsequent randomized controlled trial (RCT) on psychosocial interventions to improve treatment adherence. Finally, a separate RCT investigates the efficacy of cannabidiol as an alternative for antipsychotic treatment in patients with recent onset schizophrenia.

The aim of the current publication is to provide a review of the currently available sequential, randomized algorithm studies of this type, and to discuss the rationale for important methodological choices made for the medication algorithm of the OPTiMiSE trial. Companion articles will present reviews on other work packages of the OPTiMiSE project.

Review of Prospective Randomized Studies on Switching the Drug in Initial Nonresponders to Antipsychotics

Method
We searched Pubmed until October 29, 2014 for randomized trials in which patients with schizophrenia, schizoaffective disorder (any diagnostic criteria) had been treated prospectively with a first antipsychotic drug. Nonresponders (study defined) were subsequently randomized to either switching the antipsychotic or another pharmacological strategy. The search terms were: schizophren* AND (antipsychot* OR neurolept* OR drug OR treat*) AND (switch* OR alternativ* OR consecutiv* OR subsequent OR shift OR change) AND (nonrespon* OR nonrespon* OR not*respon* OR fail* OR resistant* OR refract* OR ineffect*), article types “clinical trials” or “randomized controlled trials.” There were no restrictions in drugs and doses used, language or when the switch was performed. The results are presented in narrative form. We excluded studies in which nonresponse was established retrospectively, because we felt that establishing nonresponse in a prospective manner is a crucial component to rule out nonspecific effects of including patients in trials. We also excluded studies which had a prospective run-in phase with the only objective to establish treatment resistance before participants were randomized to 2 other antipsychotic drugs. Such studies are not concerned with the question of whether switching the drug is effective, but rather with the efficacy of a drug in treatment resistant patients. Although the OPTiMiSE trial includes only first episode patients, we did not restrict the review to this population for which no RCTs on switching are currently available.

Results
Our search yielded 984 hits. Fourteen reports on 10 studies met the inclusion criteria and are presented more in detail in the subsequent text, for a PRISMA diagram see figure 1.

Kinon et al treated 156 inpatients with acute exacerbations of schizophrenia, schizoaffective, or schizoaffective disorder for 4 weeks with fluphenazine 20 mg/d. Inclusion criteria were not restricted to first-episode patients. From these, 58 nonresponders (defined as less than “much improved” on the Clinical Global Impression Scale [CGI] and more than “mildly ill” on 1 of the 4 psychotic items of the Brief Psychiatric Rating Scale [BPRS]) were subsequently randomized to double-blind treatment in terms of either continuing 20 mg/d fluphenazine, switching to haloperidol 20 mg/d, or to drastically increasing the fluphenazine dose to 80 mg/d (a dose that would nowadays be considered excessive). After an additional 4 weeks of treatment, irrespectively of the assigned group only 9% of the patients responded. There was no significant between-group difference in any efficacy measure. From a contemporary perspective, a major limitation of the study was that fluphenazine and haloperidol are both similar high-potency first-generation drugs. Theoretically, a switch to a drug with a more different receptor-binding profile and mechanism of action might be more promising. In addition, this study was probably underpowered to detect a difference.

Klimke et al treated 50 newly admitted, currently antipsychotic free, but not necessarily first-episode patients with schizophrenia with haloperidol 15 mg/d intravenously for 3 days after which they were classified into early responders (markedly improved or improved on a CGI like scale) or early nonresponders, and randomized both groups to either staying on haloperidol 15 mg/d orally or to switching to perazine 300 mg/d orally...
for another 3 weeks. Independently of the treatment condition, early responders improved more than early nonresponders. In contrast to the authors' initial hypothesis (that early haloperidol nonresponders would benefit from a switch to perazine), there was a trend that staying on haloperidol led to superior outcomes. The authors discussed the major limitation of their small sample size.

Shalev et al randomized 75 chronic or subchronic patients with acute exacerbations of schizophrenia to either haloperidol (a high-potency drug, target dose 20mg/d), perphenazine (mid-potency, target dose 32mg/d), or levomepromazine (low-potency, target dose 300mg/d), all given open label and flexibly dosed. Nonresponders (defined as less than 30% BPRS total score reduction from baseline) after a maximum of 8 weeks were re-randomized to 1 of the remaining 2 second-generation antipsychotics and if they still did not respond they received the third drug. The overall response was relatively high (only 16 patients (20.5%) did not respond and 7 patients (9%) discontinued the study prematurely), and perphenazine was less efficacious than the other 2 antipsychotics in secondary outcomes. The use of 3 second-generation antipsychotics makes the study more relevant to current practice where such drugs are nowadays the primary choices in many countries.

Hatta et al published 2 small studies in which they treated newly admitted, acutely ill but not necessarily first-episode patients with schizophrenia with either risperidone (study 1, n = 73, maximum dose 6mg/d) or olanzapine (study 2, n = 58, maximum dose 20mg/d) in flexible doses. The nonresponse rate at 2 weeks (≥ 4 on the CGI improvement scale) was 30% (n = 20) in the risperidone study and also 30% (n = 14) in the olanzapine study. In both studies, those who had not improved were randomized in a rater blind fashion to either switching to the other drug or to staying on the same antipsychotic for another 2 weeks. At 4 weeks, there was no significant difference in the number of patients in remission9 nor in the number of patients with at least a 50% reduction in PANSS total score between switching or staying. In both trials, the early improvers at 2 weeks responded better than the nonimprovers. But due to the small sample sizes the studies had only a pilot character.

In a subsequent rater-blinded study, the same researchers treated 156 patients with essentially the same inclusion criteria as in their previous trials22 with either risperidone (n = 74, starting dose 3mg/d) or olanzapine (n = 86, starting dose 10mg/d) at the clinicians’ discretion.23 At 2 weeks, nonresponders (CGI-I ≥ 4, n = 51) were randomized to either switching to the other drug (those on risperidone to olanzapine and those on olanzapine to risperidone) or to combining the 2 drugs for another 10 weeks. In those patients started on risperidone, there was no significant difference in the number of responders (≥ 40% PANSS total score reduction from baseline) between the switching (8%) and the combination group (29%). In those patients initially started on olanzapine, there was also no significant difference in response rates between patients switching to risperidone (25%) or combining both drugs (50%). Small sample sizes and the lack of a “stayer” control group are again limitations of this study.23
The Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) study is also relevant in this context (Lieberman et al24) and it does not have the limitation of a small sample size. About 1460 patients with chronic schizophrenia were randomized to double-blind treatment with olanzapine (7.5–30 mg/d), quetiapine (200–800 mg/d), risperidone (1.5–6 mg/d), ziprasidone (40–160 mg/d), or perphenazine (8–32 mg/d). Patients who discontinued a second-generation antipsychotic in phase I could choose between 2 other randomization pathways in phase II. In both pathways, patients could not receive the same antipsychotic as in phase I again, so that CATIE could also not address the question whether switching a drug is better than staying on the same one. In one pathway, patients were re-randomized to clozapine (considered as the intervention), olanzapine, quetiapine, or risperidone.25 In the other one, patients were allocated to ziprasidone (intervention), olanzapine, quetiapine, or risperidone.26 It was assumed that those participants who had discontinued phase I due to inefficacy would choose the clozapine pathway while those discontinued for tolerability reasons would choose the ziprasidone pathway. Unfortunately, this was not the case. Most participants who discontinued phase I (n = 444) chose the ziprasidone pathway, probably due to concerns about clozapine side effects. In the ziprasidone pathway, risperidone and olanzapine were more effective than quetiapine and ziprasidone.26 In the clozapine pathway (n = 99), clozapine was associated with the lowest discontinuation rate.25 The latter trial had the limitation that in contrast to its comparators clozapine was used open label, but it can still be used as an example for the early use of clozapine in chronic patients who had only received one previous antipsychotic during the trial. Two post hoc analyses of CATIE are also relevant here. One re-analyzed those 114 patients who had discontinued perphenazine in CATIE phase I.27 These participants responded better when they received quetiapine or olanzapine rather than risperidone in CATIE phase II. A possible explanation was that the patients randomized to quetiapine or olanzapine might have benefitted from a switch to drugs with receptor binding profiles that are more different from perphenazine than that of risperidone. It therefore provides some evidence that an antipsychotic with a different receptor binding profile should be chosen if a drug is considered in cases of insufficient efficacy. Another re-analysis of CATIE phase I, however, contradicts the latter findings, because patients taking olanzapine or risperidone before entering CATIE stayed on treatment longer in phase I if assigned to stay on the same treatment.28 However, not all patients were considered treatment resistant at study entrance and this report was not replicated by similar analysis using a slightly different approach.29 Furthermore, this analysis did not have a prospective phase and does therefore not meet our inclusion criteria.

Strongest support that switching nonresponders to a different drug is effective, stems from a recent large trial in which 628 mainly chronic patients with schizophrenia or schizoaffective disorder were treated for 2 weeks with flexibly dosed risperidone (2–6 mg/d, Kinon et al10). Those who had not shown at least a 20% reduction of the PANSS were randomized to double-blind treatment with either continuation of risperidone or a switch to olanzapine (10–20 mg/d) for an additional 10 weeks. The outcome of the switchers was slightly, but statistically significantly (P = .02) better than that of the stayers, and the difference was more pronounced in patients who were at least moderately ill at week 2.30 In any case the early improvers at 2 weeks had a clearly better outcome than the early nonimprovers, irrespectively of the subsequently assigned treatment of the latter.

Finally, the ongoing double-blind SWITCH study31 randomizes 350 newly admitted patients with acute schizophrenia, most of whom have had multiple episodes, to treatment with either amisulpride (200–800 mg/d) or olanzapine (10–20 mg/d). Nonimprovers at 2 weeks defined as <25% PANSS total score reduction from baseline are re-randomized to either staying on the same drug or switching to the other one for 6 more weeks. One of the strengths of this study is the double randomization. Re-randomizing amisulpride and olanzapine nonimprovers to the respective other drug or staying on the same drug rules out the alternative explanation that better improvement in the switching group is due to superior efficacy of the second drug rather than the switch itself.

In summary, only a few prospective studies on switching the antipsychotic in case of nonresponse to an initial drug are available and the only supportive randomized evidence with an appropriate design, namely a “stayer” control group, is currently available for switching risperidone nonresponders to olanzapine (Kimon et al10). And none of the available studies, including the SWITCH study,31 was restricted to first episode patients, making such trials a research priority (see Table 1).

**OPTiMiSE Trial Design**

The OPTiMiSE trial (http://www.optimisetrial.eu/) is performed by a consortium of 20 institutions from 13 European countries, Israel and Australia. It is funded by the European Commission under the 7th framework program. The study is coordinated by the University Medical Center (UMC) Utrecht. The trial consists of 8 work packages addressing important clinical questions in first episode schizophrenia. The work package that contains the medication algorithm addresses the following objectives:

1. To test the applicability of amisulpride as the first step in the treatment of first episode schizophrenia or schizophreniform disorder.
<table>
<thead>
<tr>
<th>Author, Country</th>
<th>Diagnosis</th>
<th>“Run-in” phase: drugs (dose), duration, blinding, number of participants</th>
<th>Randomized phase: drug groups (n), duration,blinding</th>
<th>Main resultb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinon et al, USA</td>
<td>Schizophrenia, schizoaffective, or schizoaffective disorder DSM-III-R</td>
<td>Fluphenazine 20mg/d, 4 wk, open, n = 156</td>
<td>Switch to haloperidol 20mg/d (n = 13), increase fluphenazine dose to 80mg/d (n = 16) or stay on fluphenazine 20mg/d (n = 18), 4 wk, db</td>
<td>No significant efficacy difference between groups. Only 9% responded in the randomized phase</td>
</tr>
<tr>
<td>Klimke et al, Germany</td>
<td>Acute schizophrenia, ICD-9</td>
<td>Haloperidol, 15mg/d, 3 days, open, n = 50</td>
<td>Switch to perazine 300mg/d (n = 12) or stay on haloperidol 15mg/d (n = 13), 3 wk, db</td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>Shalev et al, Israel</td>
<td>Schizophrenia, chronic, or subchronic with acute exacerbation DSM-III</td>
<td>Haloperidol (target dose 20mg/d, perphenazine (target dose 32mg/d), levomepromazine (target dose 300mg/d), open, n = 75</td>
<td>Second phase: Switch to one of the remaining antipsychotics (n = 20), 4 wk, open third phase: Switch to the remaining drug (n = 9), 4 wk, open</td>
<td>No significant difference between groups. Overall improvement rate 95%</td>
</tr>
<tr>
<td>Suzuki et al, Japan</td>
<td>Schizophrenia, DSM-IV</td>
<td>Olanzapine’ (flexible dose), quetiapine (flexible dose)’, risperidone (flexible dose)’, max. 8 wk, open, n = 78</td>
<td>Second phase: Switch to one of the remaining antipsychotics (n = 37), max. 8 wk, open. Third phase: Switch to the remaining drug (n = 19), max. 8 wk, open</td>
<td>No significant differences between drugs in the primary outcome. Quetiapine less effective than olanzapine and risperidone in secondary outcomes</td>
</tr>
<tr>
<td>Hatta et al, Japan</td>
<td>Schizophrenia, schizoaffective, or schizoaffective disorder DSM-IV</td>
<td>Risperidone (max. dose 6mg/d), 2 wk, open, n = 73</td>
<td>Risperidone (max. 6mg/d), olanzapine (max. 20mg/d) or risperidone (max. 6mg/d), n = 20, 2 wk, sb</td>
<td>No significant difference between switchers and stayers. Early responders improved more than early nonresponders</td>
</tr>
<tr>
<td>Hatta et al, Japan</td>
<td>Schizophrenia, schizoaffective, or schizoaffective disorder DSM-IV</td>
<td>Olanzapine (max. dose 20mg/d), 2 wk, sb, n = 58</td>
<td>Add the other drug or switch to the respective other drug, same doses, 10 wk, n = 51, sb</td>
<td>No significant difference between combining drugs and switching to the other drug</td>
</tr>
<tr>
<td>Hatta et al, Japan</td>
<td>Schizophrenia, schizoaffective, or schizoaffective disorder DSM-IV</td>
<td>Risperidone (starting dose 3mg/d, n = 74) or olanzapine (starting dose 10mg/d, n = 86) chosen at the physicians’ discretion, 2 wk, sb</td>
<td>Participants who discontinued phase 1 were randomized to clozapine, olanzapine, quetiapine or risperidone (patients could not receive the same drug as in phase I), n = 99, max. 18 mo, db except clozapine</td>
<td>Time to discontinuation was significantly longer for clozapine than for quetiapine and risperidone, but not longer than for olanzapine</td>
</tr>
<tr>
<td>McEvoy et al, USA</td>
<td>Schizophrenia DSM-IV</td>
<td>Olanzapine (7.5–30mg/d), perphenazine (8–32mg/d), quetiapine (200–800mg/d), risperidone (1.5–6mg/d), ziprasidone (80–160mg/d), max. 18 mo, db, n = 1493</td>
<td>Participants who discontinued phase 1 were randomized to ziprasidone, olanzapine, quetiapine, or risperidone (patients could not receive the same drug as in phase I), n = 444, max. 18 mo, db</td>
<td>Time to discontinuation was significantly longer for olanzapine and risperidone than for quetiapine and ziprasidone</td>
</tr>
<tr>
<td>Stroup et al, USA</td>
<td>Schizophrenia DSM-IV</td>
<td>Olanzapine (7.5–30mg/d), perphenazine (8–32mg/d), quetiapine (200–800mg/d), risperidone (1.5–6mg/d), ziprasidone (80–160mg/d), max. 18 mo, db, n = 1493</td>
<td>Add the other drug or switch to the respective other drug, same doses, 10 wk, n = not indicated, db</td>
<td>Switchers to olanzapine had a statistically significantly larger symptom reduction than stayers on risperidone. Ongoing study</td>
</tr>
<tr>
<td>Kinon et al, USA</td>
<td>Schizophrenia, schizoaffective, or schizoaffective disorder DSM-IV</td>
<td>Risperidone (2–6mg/d), 2 wk, open, n = 628</td>
<td>Switch to olanzapine 10–20mg/d or staying on risperidone, n = 378, 10 wk, db</td>
<td>Time to discontinuation was significantly longer for olanzapine and risperidone than for quetiapine and ziprasidone</td>
</tr>
<tr>
<td>Leucht et al, Romania</td>
<td>Schizophrenia or schizoaffective disorder DSM-IV</td>
<td>Amisulpride (200–800mg/d) or olanzapine (5–20mg/d), 2 wk, randomized, db, n = 350</td>
<td>Switching to the respective other drug or staying on the same drug, same doses, 6 wk, n = not indicated, db</td>
<td>Switchers to olanzapine had a statistically significantly larger symptom reduction than stayers on risperidone. Ongoing study</td>
</tr>
</tbody>
</table>

Note: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

We only describe the design for nonresponders in the run-in phase.

Significant means statistically significant, n = number of participants, max. = maximum, db = double-blind, sb = single-blind.

Flexible doses within the licensed range.

The participants were not necessarily discontinued due to nonresponse in CATIE.
2. To test whether nonresponders to 4 weeks treatment with amisulpride benefit from a switch to an antipsychotic with a different receptor binding profile.

3. To examine the effectiveness of early use of clozapine in nonresponding first-episode patients.

The following description focuses on methodological choices of this treatment trial which may be important for future trials. As mentioned above other work packages of OPTiMiSE (RCT on a psychosocial intervention, RCT on cannabidiol, imaging, extensive assessment of biological markers of response) will be described in companion articles.

Study Flow

Patients with a first episode of schizophrenia, schizophreniform, or schizoaffective disorder are treated for 4 weeks with open-label amisulpride in flexible doses (200–800 mg/d). Those patients who are not in remission (defined by the criteria of Andreasen et al) at 4 weeks are randomized to 6 weeks double-blind treatment with either continuation of amisulpride (200–800 mg/d) or olanzapine (5–20 mg/d). Those who are still not in remission at the end of the RCT enter a 12-week open label trial with clozapine (100–800 mg/d). Those patients who achieve symptomatic remission at the end of any study phase and all patients who leave the clozapine phase are randomized to either treatment as usual or to the psychosocial intervention to improve adherence. A subgroup of participants and healthy controls undergo an expanded MRI protocol also consisting of Magnetic Resonance Spectroscopy (MRS) with 2 follow-up scans during the study. Blood tests for the biological predictors of response are taken at each study phase. All patients are followed up for 74 weeks (see figure 2 for an overview).

Participants

Five hundred patients with a first episode of schizophrenia, schizophreniform, or schizoaffective disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) verified with the Mini International Neuropsychiatric Interview Plus (M.I.N.I. Plus; Sheehan et al) who have given written informed consent are included. The definition of first episode schizophrenia is based on the EUFEST study and relatively strict compared to other trials of this kind: participants need to be aged between 18 and 40 years, have a maximum interval between the onset of psychosis and study entry of 2 years and have used antipsychotic medication no longer than an episode of 2 weeks in the previous year or 6 weeks lifetime. These
stringent criteria are important because we assume that true first-episode patients are likely to respond better to treatment than definitions of first episode patients for whom longer pretreatment is allowed.

Rationale for Study Medication

Phase I. The choice of amisulpride as the initial drug was based on the results of the European First Episode Schizophrenia Trial (EUFEST)\textsuperscript{34} in which amisulpride turned out as one of the most effective treatments, corroborated by several meta-analyses which suggested a high efficacy and low risk for metabolic and extrapyramidal side-effects.\textsuperscript{36–38} Amisulpride is also a unique “atypical” antipsychotic, because it is a selective D2/D3 (and 5-HT\textsuperscript{7}) receptor antagonist with mesolimbic selectivity\textsuperscript{40} rather than a 5-HT2a receptor antagonist.

Phase II. To use olanzapine as the drug to which patients are randomly switched in phase II was again based on the EUFEST trial\textsuperscript{34} in which olanzapine together with amisulpride did best in the primary outcome “treatment discontinuation” due to any cause and the proportion of patients in remission applying the criteria defined by Andreasen et al.\textsuperscript{9} Moreover, olanzapine is a multireceptor antagonist and its atypical properties are mainly explained by a stronger antagonism of central serotonin than of central dopamine receptors.\textsuperscript{41,42} It thus has a very different receptor binding profile than the selective D2/D3 receptor antagonist amisulpride. This choice follows the hypothesis that nonresponders to one antipsychotic might respond to another one with a different receptor binding profile for which some evidence is available (see above\textsuperscript{27,30}).

Phase III. Clozapine is considered to be the most efficacious drug for treatment resistant schizophrenia and this has been shown in various individual RCTs\textsuperscript{43,44} and meta-analyses,\textsuperscript{37,38} one even in nonrefractory patients.\textsuperscript{36} Despite this evidence, there currently is on average a 48-month delay before eligible patients are prescribed clozapine in UK.\textsuperscript{45} As clozapine’s efficacy stands out in antipsychotic drug trials,\textsuperscript{53,54} including EUFEST,\textsuperscript{34} the notion that clozapine should be used earlier in treatment to avoid a chronic course has been put forward.\textsuperscript{8} Case series\textsuperscript{46} and 2 RCTs\textsuperscript{32,47} have even examined clozapine as the first line treatment in first-episode patients, but the 2 RCTs (1 from China,\textsuperscript{47,48} 1 from Spain\textsuperscript{32}) have shown only a faster onset of action\textsuperscript{47} and/or a longer retention in treatment\textsuperscript{32,48} than comparator drugs. Given these results, the high response rates of first-episode patients in general and the tolerability issues around clozapine, a first-line application appears to be premature, but there is a case to consider clozapine as a second-line rather than third-line option.\textsuperscript{8} This argument has been based on a prospective study in which 244 first-episode patients were treated according to a stringent algorithm.\textsuperscript{49} They first received either olanzapine or risperidone for 4 weeks. Those who had not responded were switched to the respective other drug for another 4 weeks before they were—in case of nonresponse—switched to clozapine. About 75.4% of the patients responded to the first antipsychotic prescribed, with higher response to olanzapine than to risperidone. The response rate dropped to 16.7% for the second drug, but increased again to 75% when patients were switched to clozapine. The low response rate to the second drug and the big increase in response after switching to clozapine serve as a case to use clozapine as a second line treatment to avoid unnecessary loss of time.\textsuperscript{7} In this context, OPTiMiSE will be a systematic application of clozapine in nonresponding patients within the first 12 weeks of their treatment initiation, and the second antipsychotic for those participants who were randomized to continuation of amisulpride in phase II. Clozapine levels will be determined 3 times during this 12 weeks open label phase to guarantee optimum doses in a plasma-level target range of 400–1000 ng/ml.\textsuperscript{50}

Choice of Outcomes

The primary outcome will be symptomatic remission according to the criteria of Andreasen et al.\textsuperscript{9} 8 specific symptoms (PANSS items P1, P2, P3, N1, N4, N6, G5, and G9) of schizophrenia as measured by the Positive and Negative Syndrome Scale\textsuperscript{51} are at the most only mildly present (maximum rating of “3”). Compared to the frequently used response definitions based on cutoffs of percentage reduction of the PANSS total score for which no consensus exists (20%, 30%, 40%, 50%, 60% have all been used), remission is a “harder” outcome allowing for only a minimum of symptoms that does not interfere with daily life functioning. Good clinical validity has been demonstrated (for review see Lambert et al\textsuperscript{52} and it has been shown to be a realistic goal of antipsychotic drug trials.\textsuperscript{53,54} Including EUFEST.\textsuperscript{34} The use of these remission criteria will thus facilitate translating the study results into practice guidelines.

Secondary outcome measures are all-cause discontinuation, the Positive and Negative Syndrome Scale (PANSS) total score and subscores for which raters are trained, patients’ overall severity and improvement of symptoms (CGI,\textsuperscript{16} levels of depression (Calgary Depression Scale for Schizophrenia, CDSS\textsuperscript{55}), social functioning (Personal and Social Performance Scale, PSP,\textsuperscript{56} Global Assessment of Functioning Scale, GAF\textsuperscript{57}), and quality of life with the Subjective Wellbeing under Neuroleptics Scale (SWN\textsuperscript{58}). Tolerability is examined with the UKU side effects rating scale,\textsuperscript{59} we also measure weight gain, and assess further adverse events with open interviews.

Statistical Analysis

The primary outcome will be the number of patients in symptomatic remission according to Andreasen et al.\textsuperscript{8}
The proportion of patients meeting remission criteria will be estimated at the end of phases I, II, and III. Logistic regression analyses will be used to test whether the probability of remission is significantly different between the amisulpride and olanzapine treatment arms at the end of phase II. Duration of untreated psychosis, age, and gender will be included as covariates in this analysis. The secondary outcome measure is all-cause treatment discontinuation, which will also be compared between treatment arms with survival analyses including Cox regression analyses and Kaplan-Meier functions.

Study Progress and Outlook

As of the date of submission of this manuscript, 372 participants have been included in phase I of the clinical trial, 79 have been randomized to phase II and 23 entered the clozapine phase. It is anticipated that the last patient will be included in November 2015, so that OPTiMiSE will finish in spring 2016. First results can be expected in summer 2016.

Prospective studies to examine treatment algorithms are difficult to carry out, because many patients respond to the first antipsychotic so that large sample sizes are needed for sufficient power in the subsequent phases. But given that only a handful of the 13542 controlled studies in the Cochrane register made such an attempt, most of them underpowered and none restricted to first episode patients, large studies to develop treatment algorithms are a priority to make treatment guidelines more meaningful.

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